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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/646,729	08/25/2003	Barton F. Haynes	1579-857	1174

23117 7590 12/07/2004

NIXON & VANDERHYE, PC
1100 N GLEBE ROAD
8TH FLOOR
ARLINGTON, VA 22201-4714

EXAMINER	
STUCKER, JEFFREY J	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 12/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/646,729	HAYNES ET AL.	
	Examiner	Art Unit	
	Jeffrey Stucker	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *1-18 and 20-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *25 Aug 2003*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to comply w/ sequence rules*

Applicant's election of Group III, claim 19, in the reply filed on 19 July 2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Therefore, claims 1-18 and 20-27 are withdrawn from consideration as being drawn to non-elected inventions and claim 19 is examined and rejected.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reasons set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. **Failure to fully comply in response to this Office Action will be treated as a non-responsive reply.** In view of the fact that this application is a continuation or divisional application, compliance can be fulfilled by

submitting a letter requesting the use of previously submitted sequence information. See MPEP 2422.05.

The specification and claims are objected to for failing to adhere to the requirements of the sequence rules. Applicant must append SEQ ID Nos. to all mentions of specific sequences in the specification and the claims. See 37 CFR § 1.821(d).

Claim 19 is objected to for being dependant upon a non-elected claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 19 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

"[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of

the claimed invention without 'undue experimentation.'" *Genentech Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (BdPatAppInt 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

The nature of the invention is a method for producing neutralizing antibodies to HIV in a mammal. The language of the claims encompasses treating infected patients and as such does not have support in the specification. There is insufficient disclosure to enable the claimed invention. It is well known in the art that retroviral infections in general, and HIV infections in particular, are refractory to anti-viral therapies. The obstacles to therapy of HIV are well documented in the literature. These obstacles include: 1) the extensive genomic diversity and mutation rate associated with the HIV retrovirus, particularly with respect to the gene encoding the envelope protein; 2) the fact that the modes of viral transmission include both virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert manner, as well as via free virus transmission; 3) the existence of a latent form of the virus; 4) the ability of the virus to evade immune responses in the central nervous system due to the blood-brain barrier; and 5) the complexity and variation of the pathology of HIV infection in different individuals. The existence of these obstacles establish that the contemporary state of the art would not allow one skilled in the art to use the claimed invention with a reasonable expectation of success and without undue experimentation. Further, it is well known in

the art that individuals infected with HIV produce neutralizing antibodies to the virus, yet these antibodies are not protective and do not prevent the infection from progressing to its lethal conclusion. Paul at page 1387 sets forth the difficulty and shortcomings of neutralizing antibodies. He clearly indicates that the state of the art was such that one could not produce antibodies that were truly neutralizing. Further, as taught by Fahey et al., clinical trials using a variety of immunologically based therapies have not yielded successful results in the treatment and/or prevention of HIV infection. Fahey et al. particularly discloses that monoclonal antibody therapies have not provided any clinical benefits and "it is not clear how adding these additional antibodies would make a difference" (see page 3, second column, third full paragraph). The failure of all immune-system-boosting therapies for treating AIDS is further discussed by Fox. Thus, it is clear from the evidence of Fahey et al., Paul, and Fox, that the ability to treat and/or prevent HIV infection is highly unpredictable and has met with very little success. Even though the skill in the art is high, given the lack of guidance and working examples, the quantity of experimentation necessary to practice the claimed invention is undue. The only indication of neutralizing antibodies is on page 36 of the instant specification which teaches an antibody that

is taught in the art. There is no indication that the referenced antibody was produced by the instantly claimed method. Applicants have not provided sufficient guidance to allow one skilled in the art to practice the claimed invention with a reasonable expectation of success without undue experimentation. In the absence of such guidance and evidence, the specification fails to provide an enabling disclosure. Thus, the instant invention, based on the evidence as a whole, in light of the factors articulated by the court in *In re Wands*, lacks an enabling disclosure.

The nature of the claimed invention is a broadly claimed method of inducing the production of neutralizing antibodies against HIV in a mammal which reads on a method of vaccination against HIV infection. The specification does not sufficiently support the full scope of the claimed vaccine. The state of the art is that the term "vaccine", by definition, implies a preparation intended for active immunological prophylaxis; e.g., preparations of killed microbes of virulent strains or living microbes of attenuated (variant or mutant) strains; or microbial, fungal, plant, protozoa, or metazoan derivatives or products. Although nearly any protein when inoculated can cause an immune reaction, the prophylactic nature of this reaction is

not guaranteed and has to be experimentally determined. Prophylaxis is defined as the prevention of disease or of a process that can lead to disease. For example, the *Illustrated Dictionary of Immunology* defines vaccine as a composition that stimulates protective antibodies and T cell immunity and induces active immunity. Paul in *Fundamental Immunology* teaches that vaccines were developed primarily as a prophylactic measure to prevent disease. This is achieved by use of an antigenic (immunogenic) agent to actively stimulate the immunological mechanism, or the administration of chemicals or drugs to members of a community to reduce the number of carriers of a disease and to prevent others from contracting the disease. Testing protocols are designed to test the efficacy of the vaccines which include challenge trials or natural exposure to the disease agent in an endemic area. Further, he teaches that there is not always a correlation between seroconversion and protection from disease. Given the teachings in the art, it is clear that a compound that merely induces an immune response is not sufficient but must be protective to qualify as a vaccine. See at the top of page 1312: "[T]here was not always a correlation between seroconversion and protection from disease...." There are no challenge studies with wild type virus.

The ability of a vaccine to raise a protective immune response depends on the structure of the protein epitopes. Paul teaches that to determine the immunogenicity of certain regions of a protein, knowledge of the three dimensional structure of the protein is required to determine which polypeptides in a given protein would be accessible on the surface of the protein in order for the putative antigenic determinant to be bound by the antibody. In addition, Paul states that mobility of the putative antigenic determinant within the native protein structure is also a determining factor for the binding of the antigenic determinant to an antibody. Paul points out (page 250, lines 4-8) that "Measurement of the mobility in the native protein is largely dependent on the availability of a high resolution crystal structure, so its applicability is limited to only a small subset of proteins." Riffkin et al. teaches that a single amino acid change can alter the structure of the protein dramatically. Abaza et al. teaches that mutations outside of the antigenic epitope exert an effect on the structure of the epitope. Because the structure of the protein determines its antigenicity and thereby its function as a vaccine, these structures cannot be predicted. In regards to the factors cited in the lack of utility rejection, Cohen et al. recognize other problems: "No vaccine capable of eliciting protective immunity to

HIV infection has been formulated. HIV presents a formidable challenge to immune surveillance based on many factors, including hypervariability of its principal neutralizing domain (V3) (19), concealment of critical, functional domains in the external envelope glycoprotein (gp120) behind inessential structures (20), and infection of APCs resulting in their dysfunction (21). Substantial progress has been made recently in defining neutralizing domains within the HIV envelope, and in augmenting the immune response to HIV proteins (22). Despite these important advances, an effective HIV vaccine remains elusive, we propose, because the immediate immunodeficiency accompanying HIV infection creates another obstacle to a successful vaccine (23)."

Further, clinical trials using a variety of approaches to vaccinate against HIV-1 have not yielded successful results in the treatment and/or prevention of HIV infection. Thus, it is clear from the state of the art as demonstrated by the references and the complete lack of working examples in the instant specification, it is clear that treating and/or preventing HIV infection by means of vaccines is highly unpredictable and has met with very little success even though the skill in the art is high. Therefore, the quantity of

experimentation necessary would be excessive and an undue burden on the artisan.

Applicants have not provided sufficient guidance to allow one skilled in the art to practice the claimed invention with a reasonable expectation of success and without undue experimentation. In the absence of such guidance and evidence, the specification fails to provide an enabling disclosure.

The instant invention, based on the evidence as a whole, in light of the factors articulated by the court in *In re Wands*, lacks an enabling disclosure.

No claim is allowable.

Papers related this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989).

The Group 1600 Official Fax number is: (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Stucker whose telephone number is (571)-272-0911. The examiner can normally be reached Monday to Thursday from 7:00am-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (571)-272-0902.

JEFFREY STUCKER
PRIMARY EXAMINER